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A Ring Rearrangement Approach to the Synthesis of Benzo[b]quinolizine and Benzoindolizine Architectures.**

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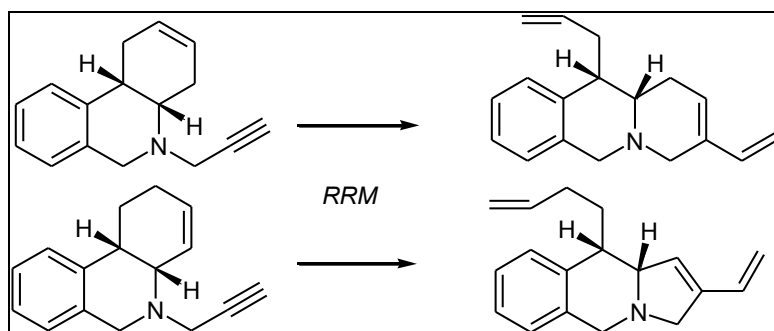
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Supplementary materials are part of this document.

Graphical abstract:



Keywords:

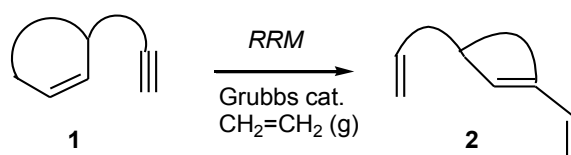
Phenanthridine; alkene; ring rearrangement metathesis; flash vacuum pyrolysis; skeletal diversity

Abstract

An efficient ring rearrangement metathesis (RRM) approach to the synthesis of benzo[*b*]quinolizine and benzoindolizine systems from *N*-propargyl-phenanthridine derivatives is reported. A novel use of flash vacuum pyrolysis (FVP) for the Boc-deprotection of acid sensitive substrates is also disclosed.

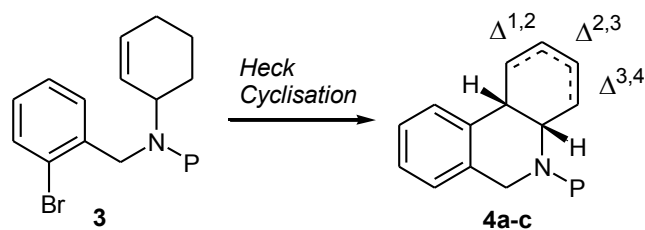
Introduction

Domino metathesis or ring-rearrangement metathesis reactions (RRM), employing combinations of RCM, ROM and cross-metathesis protocols have been developed recently,¹ and successfully applied to complex molecule synthesis.² These RRM reactions involve intramolecular metathesis of a substrate **1** containing an endocyclic olefin and a tethered exocyclic alkene or alkyne bond, to afford product **2** (e.g. Scheme 1).³ The reactions are conducted using a Grubbs metathesis catalyst under an ethylene atmosphere.

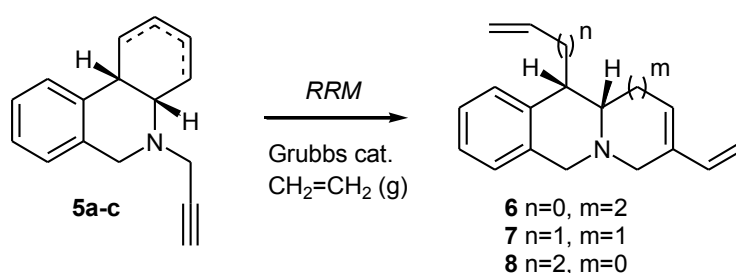


Scheme 1. Ring Rearrangement Metathesis of a Cycloalkene-yne substrate.³ Reagents and Conditions: a) Grubbs Metathesis catalyst (15 mol%), ethylene, CH₂Cl₂.

We recently disclosed novel methodology for the rapid and efficient synthesis of *cis*-ring fused phenanthridine double bond isomers **4a** ($\Delta^{1,2}$ alkene), **4b** ($\Delta^{2,3}$) and **4c** ($\Delta^{3,4}$) in excellent yield using the Heck reaction (Scheme 2).⁴ The phenanthridine core lies at the heart of many bioactive natural products including the antitumour antibiotic pancratistatin,⁵ antiviral lycorine,⁶ and the tubulin polymerisation inhibitor chelidonine.⁷ As part of our ongoing efforts towards the synthesis of a small library of natural-product-like analogues derived from this interesting core structure,⁸ we have investigated the application of an cycloalkene-yne RRM protocol to *N*-propargyl derivatives (**5a-c**) of these alkene isomers. We realised, that if successful, this would give access to three skeletally diverse products (**6** [6,6,7], **7** [6,6,6], **8** [6,6,5]) using a common metathesis process (Scheme 3).



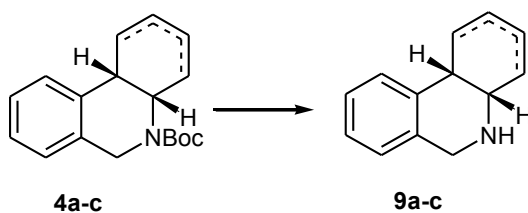
Scheme 2. Heck cyclisation approach to the phenanthridine core.⁴ P = Boc, Cbz, SO₂Me. **4a**= $\Delta^{1,2}$; **4b**= $\Delta^{2,3}$; **4c**= $\Delta^{3,4}$. Reagents and Conditions: Herrmann-Beller palladacycle (5 mol%), MeNCy₂, DMF, 140 °C; or Pd₂(dba)₃, ^tBu₃PBHF₄ (10 mol%), MeNCy₂, MeCN, r.t.→50 °C.



Scheme 3. Proposed RRM of the phenanthridine double-bond isomers. **5a**= $\Delta^{1,2}$; **5b**= $\Delta^{2,3}$; **5c**= $\Delta^{3,4}$.

Two significant obstacles to the RRM reactions of substrates **5a-c** were envisaged. Firstly, application of RRM reactions to nitrogen-containing systems are hindered by coordination of the amino group to the transition metal of the metathesis catalyst, leading to deactivation and poor reactivity.⁹ Successful approaches to counteracting this problem include the use of Lewis acids;¹⁰ amines with strongly electron-withdrawing functionality (such as sulfonamides^{11,12} or carbamates);¹² and ammonium salts.¹³ Secondly, highly strained cycloalkenes such as norbornene,^{12,14} cyclobutene,¹⁵ and cyclopentene^{3,15,16} are typically used in RRM reactions so that the ring-opening step is strongly favoured and higher conversions are obtained. There are only a few examples of the use of unstrained cycloalkene-yne substrates in RRM reactions and these tend to proceed in only low to moderate yields.^{3,11,13,17} Herein, we report the mild and efficient RRM of unstrained *N*-propargyl phenanthridines **5a-c** to afford skeletally diverse products. To the best of our knowledge, this represents the first example of the use of an unstrained and natural-product-like aminocycloalkene-yne for such a purpose.

In order to access the desired *N*-propargyl phenanthridine double bond isomers **5a-c**, we first examined the application of our Heck methodology to an *N*-propargyl derivative of precursor **3** (P = CH₂C≡CH). However, we found that the substrate was not compatible with either of the Heck cyclisation protocols we had developed in our previous work.⁴ As a result we examined direct deprotection of the isolated Boc-phenanthridine double bond isomers **4a-c**, followed by *N*-propargylation (Table 1).



Entry	Substrate	Conditions	t (h)	Conversion (%) ^a
1	4a	TFA, CH ₂ Cl ₂ , r.t.	0.5	100 ^b
2	4a	TFA, CH ₂ Cl ₂ , 0 °C	1	100 ^b
3	4a	ZnBr ₂ (2.7 eq), CH ₂ Cl ₂ , r.t.	16	100 ^b
4	4a	SnCl ₄ (4 eq), EtOAc, r.t.	16	n.d.
5	4a	CAN (0.2 eq), MeCN, 80 °C	16	n.d.
6	4a	TBAF (10 eq), THF, 80 °C	16	n.d.
7	4a	Na ₂ CO ₃ , DME/H ₂ O, 80 °C	72	0
8	4a	FVP, 600 °C	0.5	60
9	4b	FVP, 600 °C	0.5	81
10	4c	FVP, 600 °C	0.5	71

^a Determined by ¹H NMR.

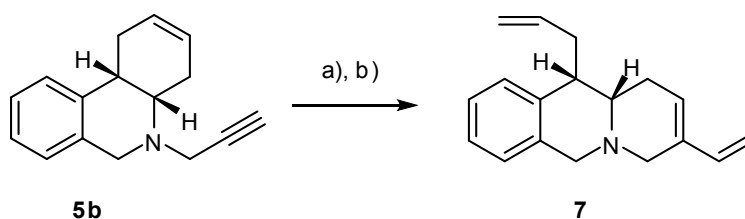
^b Significant double-bond isomerism observed.

Table 1. Boc deprotection of phenanthridines **4a-c**.

Boc-deprotection proved to be less trivial than anticipated since application of standard acidic conditions (TFA/CH₂Cl₂) to the $\Delta^{1,2}$ substrate **4a** led to both deprotection and undesired isomerism of the double bond (Table 1, entries 1 & 2). Since this would prevent testing of the RRM reaction on isolated double bond isomers a range of alternative deprotection conditions were examined using the $\Delta^{1,2}$ alkene isomer **4a**, as illustrated in Table 1. These included Lewis acid catalysis (entries 3 & 4);^{18,19} ceric ammonium nitrate (CAN) promoted oxidative radical cleavage (entry 5);²⁰ TBAF (entry 6);²¹ and Na₂CO₃ (entry 7).²² Unfortunately, none of these proved suitable, affording either deprotection with concomitant alkene isomerism (entries 1-3), or a mixture of unidentifiable products (entries 4-7). Finally we examined the use of flash vacuum pyrolysis (FVP)²³ as this has been reported to facilitate Boc-deprotection in some cases.²⁴ We were delighted to observe that exposure of $\Delta^{1,2}$ alkene **4a** to the pyrolysis tube at 600 °C under vacuum (entry 8), led to the immediate and clean removal of the Boc-group with no trace of double-bond isomerism. Gratifyingly, the deprotection conditions proved to be effective for all our alkene substrates, leading to the recovery of all three desired amines **9a-c** in good yield (60-81%). These were then readily converted to the corresponding *N*-propargyl derivatives **5a-c** using propargyl bromide and K₂CO₃ at 60 °C in acetone in good yield (57-75%).

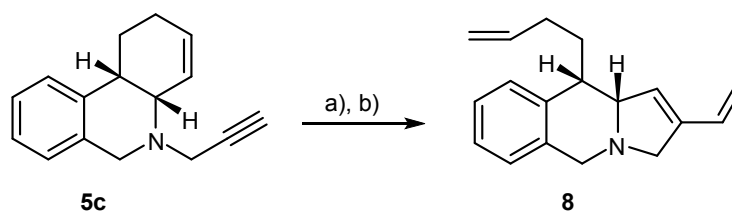
With the *N*-propargyl-phenanthridines **5a-c** in hand, we set about investigating the RRM reaction using Hoveyda-Grubbs II²⁵ as the metathesis catalyst, since its use had precedence in ROM-polymerisation reactions.²⁶ In order to prevent chelation of the amine to the Ru of the metathesis catalyst, we first

converted the *N*-propargyl phenanthridine substrates **5a-c** to the corresponding amine hydrochlorides using HCl in Et₂O. We chose to study the RRM reaction of $\Delta^{2,3}$ *N*-propargyl phenanthridine **5b** first, as this potentially afforded the most conformationally favourable product, a [6,6,6]-ring annulated benzo[*b*]quinolizine **7**. We were delighted to observe that application of the RRM conditions to this substrate led to formation of benzo[*b*]quinolizine **7** in excellent yield (Scheme 4).



Scheme 4. Reagents and Conditions a) HCl in Et₂O (2 eq); b) Hoveyda-Grubbs II (15 mol%), ethylene, CH₂Cl₂, r.t., 40 h, 71%.

Following the success of this result, we applied these conditions to the other *N*-propargyl phenanthridine substrates **5a** and **5c**. Disappointingly, we observed quantitative recovery of the starting material upon the attempted RRM of $\Delta^{1,2}$ *N*-propargyl phenanthridine **5a**. Performing the reaction at elevated temperature or with the less bulky Grubbs I catalyst had no impact on the outcome. However, we were pleased to discover that application of the Hoveyda-Grubbs II catalyst to the $\Delta^{3,4}$ *N*-propargyl-phenanthridine **5c** under an ethylene atmosphere gave complete conversion to the benzoindolizine product **8** (Scheme 5) in good yield.



Scheme 5. Reagents and Conditions a) HCl in Et₂O (2 eq); b) Hoveyda-Grubbs II (15 mol%), ethylene, CH₂Cl₂, r.t., 40 h, 80%.

In summary, we have illustrated a mild and efficient approach to the synthesis of benzo[*b*]quinolizine and benzoindolizine architectures **7** and **8** from unstrained aminocycloalkene-yne substrates using RRM

methodology. In the course of our investigations we have also illustrated a novel use of FVP for the Boc-deprotection of substrates that are susceptible to undesired acid-catalysed alkene isomerism.

General procedure for the FVP-preparation of phenanthridines 9a-c: Boc-protected phenanthridine **4** (3 mmol) was treated to FVP conditions²³ [Inlet T 140 °C, Furnace T 600 °C, P 3.2×10^{-2} Torr] for 30 mins. The crude product was purified by Kugelrohr distillation (70 °C, 0.7 Torr) to afford the desired amine **9** as a yellow oil.

General procedure for the preparation of *N*-propargyl phenanthridines 5a-c: To a solution of the appropriate phenanthridine **9** (1 mmol) in acetone (5 ml) was added anhydrous K₂CO₃ (3 mmol) and propargyl bromide (1.1 mmol). The reaction was heated at 60 °C for 2 h and then concentrated under reduced pressure. The crude product was purified by flash chromatography (CH₂Cl₂) to the desired propargyl amine **5** as a yellow oil.

(11*SR*,11*aSR*)-11-Allyl-3-vinyl-1,6,11,11*a*-tetrahydro-4*H*-pyrido[1,2-*b*]isoquinoline 7: To a solution of propargyl amine **5b** (50 mg, 0.22 mmol) in CH₂Cl₂ (1 ml) was added HCl (2 ml, 1 M in Et₂O) and the solvent was removed under reduced pressure. The resultant beige solid was dissolved in CH₂Cl₂ (10 ml) and degassed with ethylene for 10 mins. Hoveyda-Grubbs II catalyst²⁵ (21 mg, 33.6 μmol) was added and the reaction stirred under an atmosphere of ethylene for 40 h at r.t. The crude product was washed with NaOH (3 x 20 ml, 1 M aq.) and the combined organics dried (MgSO₄), concentrated under reduced pressure and purified by flash chromatography (CH₂Cl₂:MeOH, 100:0-100:1) to afford benzo[*b*]quinolizine **7** as a colourless oil (40 mg, 71%).

ν_{\max} (CHCl₃)/cm⁻¹ 2925, 1655, 1636; ¹H NMR δ (360 MHz, CDCl₃) 7.33 (1H, d, *J* 6.6), 7.18-7.14 (2H, m), 7.04-7.02 (1H, m), 6.34 (1H, dd, *J* 17.8, 10.9), 6.00-5.88 (1H, dddd, *J* 17.1, 10.3, 8.4, 5.6), 5.86-5.82 (1H, m), 5.16 (1H, dq, *J* 17.1, 1.2), 5.12 (1H, br d, *J* 10.3), 5.06 (1H, d, *J* 17.8), 4.97 (1H, d, *J* 10.9), 4.07 (1H, d, *J* 15.8), 3.78 (1H, d, *J* 15.8), 3.77 (1H, d, *J* 17.0), 3.46 (1H, d, *J* 17.0), 3.34-3.30 (2H, m), 2.91-2.84 (1H, m), 2.19-2.10 (1H, m), 2.06-1.94 (2H, m); ¹³C NMR δ (90.6 MHz, CDCl₃) 137.6 (CH), 136.8 (CH), 135.6 (C), 134.4 (C), 131.8 (C), 126.9 (CH), 126.3 (CH), 126.2 (CH), 126.0 (CH), 125.7 (CH), 116.4 (CH₂), 110.6 (CH₂), 53.8 (CH), 52.3 (CH₂), 50.0 (CH₂), 40.6 (CH), 34.2 (CH₂), 20.1 (CH₂); *m/z* (ESI+) 252 ([M+H]⁺, 98 %), 211 (15), 172 (100), 145 (8), 131 (100); HRMS (EI) Found: [M]⁺, 251.1675. C₁₈H₂₁N requires 251.1669.

(10*SR*,10*aSR*)-10-(But-3'-enyl)-2-vinyl-3,5,10,10*a*-tetrahydro-pyrrolo[1,2-*b*]isoquinoline 8: To a solution of propargyl amine **5c** (10 mg, 45 μmol) in CH₂Cl₂ (1 ml) was added HCl (2 ml, 1 M in Et₂O) and the solvent was removed under reduced pressure. The resultant beige solid was dissolved in CH₂Cl₂ (10 ml) and degassed with ethylene for 10 mins. Hoveyda-Grubbs II catalyst²⁵ (4.2 mg, 6.7 μmol) was added and the reaction stirred under an atmosphere of ethylene for 40 h at r.t. The crude product was

washed with NaOH (3 x 20 ml, 1 M aq.) and the combined organics dried (MgSO₄), concentrated under reduced pressure and purified by flash chromatography (CH₂Cl₂:MeOH, 100:0-100:5) to afford benzoindolizine **8** as a colourless oil (9 mg, 80%).

ν_{\max} (CHCl₃)/cm⁻¹ 2924, 1639, 1452; ¹H NMR δ (360 MHz, CDCl₃) 7.18-7.16 (3H, m), 7.15-7.10 (1H, m), 6.52 (1H, dd, *J* 17.5, 10.9), 5.89-5.77 (2H, m), 5.14 (1H, br d, *J* 10.9), 5.08 (1H, br d, *J* 17.5), 5.03 (1H, dq, *J* 17.1, 1.5), 4.94 (1H, dq, *J* 11.2, 1.9), 4.08 (1H, d, *J* 14.6), 3.93-3.84 (3H, m), 3.58-3.55 (1H, m), 2.96-2.92 (1H, m), 2.20-2.14 (2H, m), 1.87-1.80 (1H, m), 1.72-1.61 (1H, m); ¹³C NMR δ (90.6 MHz, CDCl₃) 140.3 (C), 139.4 (C), 138.8 (CH), 134.9 (C), 131.0 (CH), 129.0 (CH), 128.1 (CH), 126.8 (CH), 126.1 (CH), 125.8 (CH), 115.3 (CH₂), 114.6 (CH₂), 69.4 (CH), 58.3 (CH₂), 54.0 (CH₂), 41.5 (CH), 32.4 (CH₂), 30.8 (CH₂); *m/z* (EI) 251 ([M]⁺, 24%), 222 (5), 208 (14), 184 (9), 129 (27), 125 (22), 84 (100); HRMS (EI) Found: [M]⁺, 251.1665. C₁₈H₂₁N requires 251.1669.

Full characterisation of *N*-propargyl cyclisation precursor **3** (P = CH₂C≡CH), Boc-phenanthridines **4a-c**, *N*-propargyl phenanthridines **5a-c** and deprotected phenanthridines **9a-c** are included in the supporting information.

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Supporting information

All non-aqueous reactions were carried out under an atmosphere of nitrogen using flame- or oven-dried glassware. Unless otherwise noted, starting materials and reagents were obtained from commercial suppliers and were used without further purification. CH_2Cl_2 was distilled from calcium hydride. Flash column chromatography was carried out on Merck Kieselgel 60 (Merck 9385) under positive pressure by means of an air line or hand pump. TLC was performed on Merck 60F254 (0.25 mm) glass silica plates and visualised by ultraviolet (UV) light and/or KMnO_4 stain. IR spectra were measured on a Biorad FTS-7 or Perkin-Elmer Paragon 1000 FT-IR spectrometer as thin films unless otherwise stated. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC250 or Bruker DPX360 instrument. J values are in Hz. Electrospray (ESI) mass spectra were obtained using a Thermo MAT 900 XP mass spectrometer, and fast atom bombardment (FAB) mass spectra were obtained using a Kratos MS50TC mass spectrometer both at The University of Edinburgh. High performance liquid chromatography (HPLC) was carried out using a Gilson instrument fitted with a refractive index detector, using a microsorb 100-5 Si column (length 250 mm, id 21.4 mm, particle size 5 μm). All HPLC samples were filtered through 0.45 μm nylon syringe filters prior to analysis. A standard flow rate of 10.0 ml min⁻¹ was used. All solvents used for HPLC were filtered prior to use.

(2-Bromo-benzyl)-cyclohex-3-enyl-prop-2-ynyl-amine 3 (P = $\text{CH}_2\text{C}\equiv\text{CH}$): To a suspension of *N*-(2-bromobenzyl)-cyclohex-2-enyl-amine hydrochloride⁴ (100 mg, 0.33 mmol) in DMF (5 ml) at r.t. was added K_2CO_3 (137 mg, 1.00 mmol) and the reaction stirred for 10 mins. Propargyl bromide (148 μl , 80 % by w/w , in toluene, 1.66 mmol) was added dropwise and the reaction stirred for 16 h. The reaction was diluted with Et_2O (20 ml) and washed with NaCl (3 x 20 ml, sat. aq.), and the combined organics were dried (MgSO_4) and concentrated under reduced pressure. The resultant oil was purified using flash chromatography (hexane:EtOAc, 100:15) to afford propargyl amine **3** (P = $\text{CH}_2\text{C}\equiv\text{CH}$) as a colourless oil (103 mg, 99%).

ν_{max} (CHCl_3)/cm⁻¹ 3299(C \equiv C-H), 2931, 1439, 1025; ^1H NMR δ (250 MHz, CDCl_3) 7.59 (1H, d, J 7.6, ArH), 7.56 (1H, dd, J 7.9, 1.2, ArH), 7.29 (1H, td, J 7.4, 1.2, ArH), 7.10 (1H, td, J 7.8, 1.4, ArH), 5.89-5.76 (2H, m, CH=CH), 3.91 (1H, d, J 15.0, $\text{CH}_\text{X}\text{H}_\text{Y}\text{Ar}$), 3.82 (1H, d, J 15.0, $\text{CH}_\text{X}\text{H}_\text{Y}\text{Ar}$), 3.56-3.53 (1H, m, CHN), 3.38 (2H, d, J 2.4, $\text{CH}_2\text{C}\equiv\text{CH}$), 2.23 (1H, t, J 2.4, $\equiv\text{CH}$), 2.03-1.84 (4H, m, 2x CH_2), 1.69-1.44 (2H, m, CH_2); ^{13}C NMR δ (62.9 MHz, CDCl_3) 138.7 (C), 132.5 (CH), 130.6 (CH), 130.4 (CH), 129.7 (CH), 128.1 (C), 127.1 (CH), 124.2 (C), 81.4 (C), 72.2 (CH), 57.6 (CH), 52.9 (CH_2), 39.3 (CH_2), 25.2 (CH_2), 24.8 (CH_2), 21.2 (CH_2); m/z (EI) 305 ($[\text{}^{81}\text{BrM}]^+$, 19 %), 303 ($[\text{}^{79}\text{BrM}]^+$, 19), 277 (64), 275 (65), 251 (33), 249 (35), 213 (42), 171 (97), 169 (100), 106 (85); HRMS (EI) Found: $[\text{}^{79}\text{BrM}]^+$, 303.0618. $\text{C}_{16}\text{H}_{18}\text{N}^{79}\text{Br}$ requires 303.0617.

(4aSR,10bSR)-4,4a,6,10b-Tetrahydro-3H-phenanthridine-5-carboxylic acid *tert*-butyl ester 4a ($\Delta^{1,2}$ isomer)⁴: R_t [hexane:EtOAc, 92:8] 17 min; ν_{max} (CHCl_3)/cm⁻¹ 3026, 1693 (C=O), 1258, 913, 745; ^1H

NMR δ (360 MHz, 323 K, CDCl_3) 7.30 (1H, d, J 7.5, ArH), 7.25-7.17 (2H, m, 2xArH), 7.12 (1H, d, J 7.2, ArH), 6.17-6.13 (1H, m, CHCH=CH), 5.87-5.83 (1H, m, CH=CHCH₂), 4.71 (1H, d, J 16.5, CH_XH_YAr), 4.41 (1H, br s, NCHCH), 4.39 (1H, d, J 16.5, CH_XH_YAr), 3.57 (1H, br s, NCHCH), 2.31-2.27 (1H, m, CH_AH_B), 2.15-2.05 (1H, m, CH_AH_B), 1.79-1.69 (1H, m, CH_CH_D), 1.61-1.40 (10H, m, 3 x CH₃+CH_CH_D); ¹³C NMR δ (90.0 MHz, 323 K, CDCl_3) 155.0 (C), 137.8 (C), 132.5 (C), 128.3 (CH), 128.1 (C), 127.6 (CH), 127.3 (CH), 126.8 (CH), 126.1 (CH), 125.9 (CH), 79.6 (C), 43.5 (CH₂), 37.3 (CH), 28.5 (3xCH₃), 25.3 (CH₂), 24.2 (CH₂); m/z (FAB, THIOG) 284 ([M-H]⁺, 44 %), 228 (66), 184 (49), 130 (25); HRMS (FAB, THIOG) Found: [M-H]⁺ 284.1643. C₁₈H₂₂NO₂ requires 284.1650.

(4aSR,10bSR)-4,4a,6,10b-Tetrahydro-1H-phenanthridine-5-carboxylic acid *tert*-butyl ester 4b ($\Delta^{2,3}$ isomer)⁴: R_t [hexane:EtOAc, 92:8] 18 min; ν_{max} (CHCl₃)/cm⁻¹ 3352, 1699 (C=O), 1392, 1367, 1167; ¹H NMR δ (250 MHz, CDCl_3) 7.24-7.16 (4H, m, 4xArH), 5.70-5.66 (1H, m, CHCH₂CH=), 5.45-5.37 (1H, m, NCHCH₂CH=), 4.68-4.66 (3H, m, CH₂Ar+NCHCH₂), 3.32-3.18 (1H, m, CHCH₂), 2.86 (1H, dd, J 18.0, 4.5, CH_AH_B), 2.67-2.54 (1H, m, CH_AH_B), 2.28-2.16 (1H, m, CH_CH_D), 1.65-1.52 (10H, m, 3xCH₃+CH_CH_D); ¹³C NMR δ (62.9 MHz, CDCl_3) 154.8 (C), 136.4 (C), 133.9 (C), 126.6 (CH), 126.4 (CH), 126.1 (CH), 125.4 (CH), 124.8 (CH), 123.7 (CH), 79.6 (C), 50.3 (CH), 44.6 (CH₂), 35.5 (CH), 28.5 (3xCH₃), 26.2 (CH₂); m/z (EI) 285 ([M]⁺, 2 %), 231 (32), 175 (100), 130 (22); HRMS (EI) Found: [M]⁺ 285.1726. C₁₈H₂₃NO₂ requires 285.1723.

(4aSR,10bSR)-2,4a,6,10b-Tetrahydro-1H-phenanthridine-5-carboxylic acid *tert*-butyl ester 4c ($\Delta^{3,4}$ isomer)⁴: R_t [hexane:EtOAc, 92:8] 16 min; ν_{max} (CHCl₃)/cm⁻¹ 3359, 1695 (C=O), 1400, 1367; ¹H NMR δ (250 MHz, CDCl_3) 7.37 (1H, d, J 7.5, ArH), 7.26-7.13 (2H, m, 2xArH), 7.07 (1H, d, J 7.0, ArH), 5.72-5.65 (1H, m, CH₂CH=CH), 5.52 (1H, d, J 11.0, CH=CHCH), 5.08 (1H, br s, NCH), 4.86 (1H, d, J 17.0, CH_XH_YAr), 4.24 (1H, d, J 17.0, CH_XH_YAr), 3.30 (1H, br s, CHCH₂), 2.45-2.37 (1H, m, CH_ACH_B), 2.08-1.94 (1H, m, CH_AH_B), 1.95-1.81 (2H, m, CH₂), 1.50 (9H, s, 3xCH₃); ¹³C NMR δ (62.9 MHz, CDCl_3) 154.8 (C), 135.1 (C), 133.9 (C), 130.8 (CH), 127.6 (CH), 126.5 (2xCH), 125.8 (CH), 125.6 (CH), 79.8 (C), 50.0 (CH), 42.6 (CH₂), 34.5 (CH), 28.4 (3xCH₃), 25.0 (CH₂), 20.2 (CH₂); m/z (EI) 285 ([M]⁺, 2 %), 229 (77), 228 (100), 184 (32), 175 (48); HRMS (EI) Found: [M]⁺ 285.1720. C₁₈H₂₃NO₂ requires 285.1723.

(4aSR,10bSR)-3,4,4a,5,6,10b-Hexahydro-phenanthridine 9a: Flash vacuum pyrolysis of Boc-protected $\Delta^{1,2}$ isomer phenanthridine **4a** [500 mg, T_f 600 °C, T_i 140 °C, P 3.2 x 10⁻² Torr, t 0.5 h], followed by Kugelrohr distillation (70 °C, 0.7 Torr) afforded amine **9a** as a yellow oil (193 mg, 60%).

ν_{max} (CHCl₃)/cm⁻¹ 3274 (NH), 3019, 2920, 1671 (C=C), 1449, 1260 (CN); ¹H NMR δ (360 MHz, CDCl_3) 7.22-7.21 (2H, m, 2xArH), 7.17-7.14 (1H, m, ArH), 7.03 (1H, d, J 7.5, ArH), 5.74-5.71 (1H, m, CH=CH), 5.66-5.62 (1H, m, CH=CH), 4.12 (1H, d, J 16.3, CH_XH_YAr), 4.04 (1H, d, J 16.3, CH_XH_YAr), 3.36 (1H, br s, NCHCH), 3.32-3.28 (1H, m, NCHCH), 2.25-2.03 (2H, m, CH₂), 2.03-1.89 (2H, m, CH₂); ¹³C NMR δ (90.6 MHz, CDCl_3) 138.4 (C), 135.7 (C), 130.2 (CH), 129.1 (CH), 126.4 (CH), 125.8

(CH), 125.7 (2xCH), 50.4 (CH), 48.3 (CH₂), 38.0 (CH), 27.4 (CH₂), 20.0 (CH₂); *m/z* (EI) 185 ([M]⁺, 77 %), 170 (21), 168 (18), 131 (38), 130 (72), 128 (46); HRMS (EI) Found: [M]⁺, 185.1196. C₁₃H₁₅N requires 185.1199.

(4aSR,10bSR)-1,4,4a,5,6,10b-Hexahydro-phenanthridine 9b: Flash vacuum pyrolysis of Boc-protected Δ^{2,3} isomer phenanthridine **4b** [900 mg, T_f 600 °C, T_i 140 °C, P 3.2 x 10⁻² Torr, t 0.5 h], followed by Kugelrohr distillation (70 °C, 0.7 Torr) afforded amine **9b** as a yellow oil (500 mg, 81%).

*ν*_{max} (CHCl₃)/cm⁻¹ 3284 (NH), 3021, 2902, 1654 (C=C), 1453, 1260 (CN); ¹H NMR δ (360 MHz, CDCl₃) 7.17-7.13 (2H, m, 2xArH), 7.09-7.02 (2H, m, ArH), 5.73-5.66 (2H, m, CH=CH), 4.24 (1H, d, *J* 16.5, CH_XH_YAr), 4.15 (1H, d, *J* 16.5, CH_XH_YAr), 3.23 (1H, br d, *J* 4.0, NCHCH), 2.81 (1H, ddd, *J* 10.1, 6.4, 2.7, NCHCH), 2.65-2.59 (1H, m, CH_AH_B), 2.34-2.28 (1H, m, CH_AH_B), 2.15-2.10 (2H, m, CH₂); ¹³C NMR δ (90.6 MHz, CDCl₃) 141.0 (C), 134.2 (C), 128.2 (CH), 126.0 (CH), 125.9 (CH), 125.8 (CH), 124.7 (CH), 124.1 (CH), 49.9 (CH), 48.5 (CH₂), 35.3 (CH), 31.9 (CH₂), 30.1 (CH₂); *m/z* (EI) 185 ([M]⁺, 10 %), 130 (100); HRMS (EI) Found: [M]⁺, 185.1202. C₁₃H₁₅N requires 185.1199.

(4aSR,10bSR)-1,2,4a,5,6,10b-Hexahydro-phenanthridine 9c: Flash vacuum pyrolysis of Boc-protected Δ^{3,4} isomer phenanthridine **4c** [320 mg, T_f 600 °C, T_i 140 °C, P 3.2 x 10⁻² Torr, t 0.5 h], followed by Kugelrohr distillation (70 °C, 0.7 Torr) gave amine **9c** as a yellow oil (190 mg, 71%).

*ν*_{max} (CHCl₃)/cm⁻¹ 3283 (NH), 3020, 2902, 1654 (C=C), 1453, 1260 (CN); ¹H NMR δ (360 MHz, CDCl₃) 7.23-7.13 (3H, m, 3xArH), 7.03 (1H, d, *J* 7.2, ArH), 5.96-5.85 (2H, m, CH=CH), 4.05 (1H, d, *J* 16.6, CH_XH_YAr), 4.00 (1H, d, *J* 16.9, CH_XH_YAr), 3.46 (1H, br s, NCHCH), 2.74 (1H, dt, *J* 12.6, 3.6, NCHCH), 2.22-1.62 (4H, m, 2xCH₂); ¹³C NMR δ (90.6 MHz, CDCl₃) 139.3 (C), 135.8 (C), 130.0 (CH), 129.2 (CH), 128.3 (CH), 126.1 (CH), 125.7 (CH), 125.5 (CH), 50.7 (CH), 48.2 (CH₂), 36.5 (CH), 27.5 (CH₂), 25.8 (CH₂); *m/z* (EI) 185 ([M]⁺, 10 %), 130 (100); HRMS (EI) Found: [M]⁺, 185.1202. C₁₃H₁₅N requires 185.1199.

(4aSR,10bSR)-5-(Prop-2'-ynyl)-3,4,4a,5,6,10b-hexahydro-phenanthridine 5a: To a solution of amine **9a** (150 mg, 0.81 mmol) in acetone (5 ml) was added K₂CO₃ (368 mg, 2.67 mmol), and propargyl bromide (100 μl, 80 % w/w in toluene, 0.89 mmol). The reaction was heated at 60 °C for 2 h and then concentrated under reduced pressure. Flash chromatography (CH₂Cl₂) afforded propargyl amine **5a** as a yellow oil (103 mg, 57%).

*ν*_{max} (CHCl₃)/cm⁻¹ 3290 (C≡C-H), 2925, 1696; ¹H NMR δ (250 MHz, CDCl₃) 7.27-7.10 (3H, m, 3xArH), 7.10 (1H, d, *J* 7.2, ArH), 5.79 (2H, s, CH=CH), 4.01 (1H, d, *J* 15.0, CH_XH_YAr), 3.83 (1H, dd, *J* 17.4, 2.4, CH_PH_QC≡CH), 3.81 (1H, d, *J* 15.0, CH_XH_YAr), 3.56 (1H, dd, *J* 17.4, 2.4, CH_PH_QC≡CH), 3.56 (1H, br s, NCHCH), 3.16 (1H, br s, NCHCH), 2.28 (1H, t, *J* 2.4, ≡CH), 2.14-2.00 (3H, m, CH₂+CH_AH_B), 1.87-1.75 (1H, m, CH_AH_B); ¹³C NMR δ (62.9 MHz, CDCl₃) 137.3 (C), 133.8 (C), 129.8 (CH), 128.0 (CH), 126.5 (CH), 126.4 (CH), 126.1 (CH), 125.6 (CH), 78.3 (C), 73.4 (CH), 53.8 (CH),

53.4 (CH₂), 42.3 (CH₂), 39.2 (CH), 23.2 (CH₂), 21.9 (CH₂); *m/z* (EI) 223 ([M]⁺, 59 %), 222 (100), 208 (16), 184 (17), 168 (36), 140 (34); HRMS (EI) Found: [M]⁺, 223.1354. C₁₆H₁₇N requires 223.1356.

(4aSR,10bSR)-5-(Prop-2'-ynyl)-1,4,4a,5,6,10b-hexahydro-phenanthridine 5b: To a solution of amine **9b** (50 mg, 0.27 mmol) in acetone (2 ml) was added K₂CO₃ (112 mg, 0.81 mmol) and propargyl bromide (33 μ l, 80 % w/w in toluene, 0.30 mmol). The reaction was heated at 60 °C for 2 h and then concentrated under reduced pressure. Flash chromatography (CH₂Cl₂) afforded propargyl amine **5b** as a colourless oil (45 mg, 75%).

ν_{\max} (CHCl₃)/cm⁻¹ 3292 (C \equiv C-H), 2925, 1663, 1604, 1430; ¹H NMR δ (360 MHz, CDCl₃) 7.17-7.14 (2H, m, 2xArH), 7.12-7.08 (2H, m, 2xArH), 5.76-5.72 (1H, m, CH=CH), 5.67-5.63 (1H, m, CH=CH), 4.10 (1H, d, *J* 15.2, CH_XH_YAr), 3.88 (1H, d, *J* 15.2, CH_XH_YAr), 3.75 (1H, dd, *J* 15.3, 2.3, CH_PH_QC \equiv CH), 3.49 (1H, dd, *J* 15.3, 2.3, CH_PH_QC \equiv CH), 3.08-3.05 (1H, m, NCHCH), 2.99 (1H, td, *J* 7.9, 2.4, NCHCH), 2.53-2.43 (1H, m, CH_AH_B), 2.38-2.13 (3H, m, CH₂+CH_AH_B), 2.26 (1H, t, *J* 2.3, \equiv CH); ¹³C NMR δ (90.6 MHz, CDCl₃) 140.2 (C), 134.0 (C), 127.0 (CH), 126.5 (CH), 126.3 (CH), 125.8 (CH), 125.7 (CH), 122.9 (CH), 78.3 (C), 73.4 (CH), 54.4 (CH₂), 53.3 (CH), 42.2 (CH₂), 37.6 (CH), 31.4 (CH₂), 26.4 (CH₂); *m/z* (EI) 223 ([M]⁺, 6 %), 222 (6), 168 (100), 129 (25); HRMS (EI) Found: [M]⁺, 223.1350. C₁₆H₁₇N requires 223.1356.

(4aSR,10bSR)-5-(Prop-2'-ynyl)-1,2,4a,5,6,10b-hexahydro-phenanthridine 5c: To a solution of amine **9c** (52 mg, 0.28 mmol) in acetone (5 ml) was added K₂CO₃ (116 mg, 0.84 mmol) and propargyl bromide (35 μ l, 80% w/w in toluene, 0.31 mmol). The reaction was heated at 60 °C for 2 h and then concentrated under reduced pressure. Flash chromatography (CH₂Cl₂) afforded propargyl amine **5c** as a yellow oil (37 mg, 60%).

ν_{\max} (CHCl₃)/cm⁻¹ 3291 (C \equiv C-H), 3027, 2925, 1663; ¹H NMR δ (360 MHz, CDCl₃) 7.20-7.04 (3H, m, 3xArH), 7.05 (1H, d, *J* 7.3, 2xArH), 6.02-5.93 (2H, m, CH=CH), 3.98 (1H, d, *J* 15.1, CH_XH_YAr), 3.82 (1H, dd, *J* 17.2, 2.3, CH_PH_QC \equiv CH), 3.78 (1H, d, *J* 15.1, CH_XH_YAr), 3.51 (1H, dd, *J* 17.2, 2.4, CH_PH_QC \equiv CH), 3.26 (1H, br s, NCHCH), 2.84 (1H, dt, *J* 11.2, 3.5, NCHCH), 2.27 (1H, t, *J* 2.3, \equiv CH), 2.16-2.04 (3H, m, CH₂+CH_AH_B), 1.85-1.76 (1H, m, CH_AH_B); ¹³C NMR δ (90.6 MHz, CDCl₃) 138.8 (C), 134.5 (C), 132.1 (CH), 128.2 (CH), 126.2 (CH), 126.0 (CH), 125.6 (CH), 125.5 (CH), 78.5 (C), 73.1 (CH), 54.0 (CH₂), 54.0 (CH), 42.3 (CH₂), 38.0 (CH), 27.7 (CH₂), 25.7 (CH₂); *m/z* (EI) 223 ([M]⁺, 30 %), 222 (47), 194 (10), 169 (100), 129 (15).